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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/436,339	07/13/95	PAPAYANNOPOULOU	T B173-CIP

EXAMINER: JOHNSON, N

ART UNIT	PAPER NUMBER
1806	8

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DATE MAILED: 02/26/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-28 is/are pending in the application.
Of the above, claim(s) 15-28 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-14 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

1. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the restriction requirement is improper, as it fails to establish that the inventions are independent and distinct. This is not found persuasive. The inventions are distinct, each from the other because the methods of Groups I-IV differ in the method objectives, method steps and parameters and in the reagents used. The method of Group I is a method for the peripheralization of cells. Groups II-IV are methods of treatment that involve additional method steps and reagents. For example, the method of treating cancer and AIDS in Groups II and III involves the step of administering myeloblative chemotherapy or radiotherapy to the patient, while Group IV involves the method step of transfecting peripheralized cells with a retroviral vector. Additionally, Groups II-IV are three different methods utilizing the peripheralized cells that result from the method of Group I. For these reasons the restriction requirement is deemed to be proper and is adhered to. The requirement is still deemed proper and is therefore made FINAL.

2. Claims are 15-28 are withdraw from examination.

Claims 1-14 are examined on the merits.

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825.

Applicant states that this application is the national stage of the international application PCT/US93/11060, which is in compliance with the requirements of 37 C.F.R. §§ 1.821-1.825. Thus, the applicant need not submit a new computer readable form of the Sequence Listing in this application which contains the same sequence disclosures as PCT/US93/11060. However, the applicant must request in writing that the CRF in the parent case be used to prepare a file for the offspring; and applicant must submit a statement that the paper copy of the Sequence Listing in the offspring is identical to the computer readable form submitted in the parent case.

APPLICANT IS GIVEN THE RESPONSE PERIOD OF THIS OFFICE ACTION WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. Applicant is requested to return a copy of the attached Notice to Comply with the response.

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 to 07/977,702 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the earlier filed application(s) in the first sentence of the specification (37 CFR 1.78).

5. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

6. The disclosure is objected to because of the following informalities: Subfigures 1A-1C, 3A-3B, 4A-4B, 5A-5B, 6A-6B, 7A-7B and 8A-8B are not separately described in the Brief Description of the Drawings. Appropriate correction is required.

7. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-2 and 14 are vague and indefinite in the recitation "blocking agent." The specific function blocked is unclear.

b. Claims 7-9 are vague and indefinite in the recitation of laboratory abbreviations for cytokines, especially T-SCF and SCPF. Use of the full terminology is recommended.

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and an enabling specification commensurate with the scope of the claims.

a. Claims 1 and 2 are drawn to "administering a blocking agent of VLA-4 antigen," while claim 2 is drawn to blocking agents selected from the group consisting of anti-VLA-4 or anti-VCAM-1 antibodies, fibronectin, soluble VCAM-1, bifunctional VCAM-1/Ig fusion proteins and VCAM-1 peptides (and variants of the specific products listed).

The specification demonstrates such peripheralization with only one blocking agent, the specific murine monoclonal anti-VLA-4 antibody, HP1/2 (see Figures 1 and 3). The specification does not provide instruction for the identification and use of "blocking agents" as broadly claimed. The identification of other blocking agents as broadly claimed would be unpredictable and would require undue experimentation of one of skill in the art. Neither does the specification provide a demonstration of the efficacy in the claimed peripheralization method of the wide range of "blocking agents" recited in claim 2. There citation of literature that indicates these various products bind or interact with either VLA-4 or VCAM-1 does not provide adequate nexus to one of skill in the art that they all would effectively mediate the claimed peripheralization method.

In addition, as demonstrated in Pulido et al., there are at least three different VLA-mediated adhesion functions which correlate with three distinct VLA-4 epitopes, as defined by monoclonal antibodies (see abstract). Thus, there is reason to believe that specific epitopes of

VLA-4 mediate VLA-4's adhesion functions and to believe that not all anti-VLA-4 monoclonal antibodies will be capable of the peripheralization effect observed with the HP1/2 treatment of the instant application. Papayannopoulou and Nakamoto (PNAS 90:9374, 1993) support this concern, with the reference to "nonblocking versus attachment-blocking anti-VLA-4 antibody" (see top of column 1, p. 9378).

b. Claims 4-9 are drawn to the administration of "a stimulating agent" and claims 7-9 are drawn to a cytokine stimulating agent "selected from the group of consisting of G-CSF, stem cell factor, GM-CSF, M-CSF, T-CSF, SCPF, IL-1, IL-2, IL-3, IL-4, IL-6 and IL-11." The specification teaches only the administration of cytokines as the specific stimulating agent (see pp.14-15) and does not provide instruction for the identification and use of the broadly claimed "stimulating agent." The identification of other such agents with the claimed effects would be unpredictable and would require undue experimentation would be required of one of skill in the art. The specification demonstrates the effectiveness of only GM-CSF in the claimed method. As documented by "T-Cell-Derived Lymphokines," it is well known in the art that the term "cytokine" represents a very large group of factors of different origins, with a very wide range of functional activities. For example Il-2 promotes growth of activated T-cells (Table 2), GM-CSF causes a dose dependent rise in peripheral granulocytes (p. 628, col.2) and IL-6 induces Ig production. U.S. Patent No. 5,206,345 is cited, which indicates that the cytokines IL-1, IL-2 and IL-4 induce endothelium to be more adhesive for lymphocytes (col.6, lines 21-28 and col 9, lines 7-9) Thus, absent evidence to the contrary, one of skill in the art would not expect would

not expect the broad list of cytokines claimed, except GM-CSF to effectively mediate the peripheralization of cells.

One of skill in the art could not practice the claimed invention commensurate with the scope of the claims with a reasonable expectation of success and without undue experimentation, using the specification for guidance.

9. Claims 1-14 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Simmons (Blood 80: 388, July 15, 1992) or Teixido (J. Clin. Invest. 90: 358, August 1992) . Both Simmons and Teixido disclose a method using of anti-VLA-4 antibodies to block the adhesion of CD^{34} cells to bone marrow stromal cells *in vitro*, which is broadly interpreted to be a form of "peripheralization."

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simmons (Blood 80: 388, July 15, 1992) or Teixido (J. Clin. Invest. 90: 358, August 1992) in view of Haas (Exp. Hematol. 18:94-98, 1990). The teachings of Simmons and Teixido, on a method using anti-VLA-4 antibodies to peripheralize CD^{34} cells has been previously discussed in the above paragraph. Neither Simmons or Teixido teaches the use of a stimulating agent, GM-CSF *in vivo*. However, Haas teaches the *in vivo* use of GM-CSF in the preparation of hematopoietic stem cells. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use *in vivo* administration of GM-CS, as taught in Haas, in the peripheralization method of either of Simmons or Teixido. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Haas, on the increased number of circulating stem cells that result from GM-CSF administration (see col.2, p.94).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy A. Johnson, Ph.D. whose telephone number is (703) 305-5860. The

examiner can normally be reached on Monday-Friday from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax number for the group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800

Nancy A. Johnson, Ph.D.

February 18, 1997